UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

IN RE VALSARTAN, LOSARTAN, AND IRBESARTAN PRODUCTS LIABILITY LITIGATION	**MDL No. 2875**
THIS DOCUMENT RELATES TO ALL CASES	**HON. ROBERT B. KUGLER** **CIVIL NO. 19-2875 (RBK)**

PLAINTIFFS' BRIEF IN SUPPORT OF *DAUBERT* MOTION TO PRECLUDE OPINIONS OF DEFENSE EXPERT ALI AFNAN, PH.D.

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PRELIMINARY STATEMENT

This motion arises against the backdrop of the disturbing contamination of the generic hypertension medication valsartan. As stated by this Court: "The Valsartan MDL arose from an extensive Food and Drug Administration ["FDA"] recall in the U.S. of generic hypertensive, prescription drugs ["Valsartan" or "Valsartan-containing drugs" or "VCDs"]. To be clear, as used herein, the term "VCD" refers to valsartan-containing drugs that were contaminated with probable genotoxic human carcinogens in the form of nitrosamines, N-nitrosodimethylamine ("NDMA") and N- N-nitrosodiethylamine ("NDEA")." (ECF 2261, at 2). As recognized by this Court: "It is further incontrovertible in the morass of factual and legal arguments here that the contamination resulted from defendants' non-compliance of cGMPs at some level." (*Id.* at 21).

Ali Afnan, Ph.D. [redacted] It also runs counter to a smoking gun email written by a ZHP organic chemist whose job it was to identify impurities and their mechanisms of formation in drug substances, written almost one year before the contamination was finally disclosed. The July 27, 2017 email stated that there was NDMA in

valsartan and correctly identified the root cause for the formation of NDMA—the quenching of sodium azide with sodium nitrite.

Dr. Afnan's opinions cannot stand because they are not supported by a valid methodology.

[redacted]

Dr. Afnan's conclusory opinions stand in weak juxtaposition to the facts, including the findings by the FDA against ZHP. [redacted]. Dr. Afnan's opinions are unsupported by any properly applied, accepted methodology, requiring preclusion of his opinions.

STATEMENT OF FACTS

Ali Afnan, Ph.D. [redacted]

[redacted] (Afnan 2/8/2023 Dep. Tr. 13:24-18, 17:7-12, Ex. 1).[1]

[redacted] (*Id.* at 63:8-11, 63:17-64:2). [redacted] (*Id.* at 158:3-13, 168:11-171:11). [redacted] (*Id.* at 173:11-16).

ZHP developed its offending manufacturing processes—the TEA with sodium nitrite quenching and Zinc Chloride processes—for financial reasons, to increase yield and lower cost.[2] This set the stage for ZHP to "dominate the world market" for generic valsartan, in the words of ZHP Executive Vice President, Jun Du, who stated this during an interview with an FDA investigator. (PRINSTON00162373, Ex. 3).

ZHP has admitted that it performed no scientific analysis of the potential risks of the formation of genotoxic impurities as a result of these processes. ZHP has stipulated that:

[1] Unless otherwise noted, all exhibits are included in Adam M. Slater's certification in support of this motion.

[2] [redacted] (PRINSTON0076115-116, Ex. 2).

1. ZHP states that it was required to perform a risk assessment in connection with the process change to the zinc chloride process. ZHP further states the following:

    a. ZHP states that the scientific research relied on to use DMF as part of the zinc chloride process did not include scientific research into the potential decomposition products of DMF under the conditions of the zinc chloride process.

    b. The risk assessment of DMF did not specifically evaluate whether DMF was degrading to yield dimethylamine as part of the zinc chloride process.

    c. Therefore, there is no document from Shanghai SynCores or ZHP that documents that potential degradation of DMF as part of the zinc chloride process was evaluated as part of the risk assessment for the zinc chloride process.

    d. ZHP states that it did not perform a risk assessment on the potential degradation of DMF because it did not realize that DMF would degrade in the way it ultimately degraded in the zinc chloride manufacturing process of valsartan. **ZHP is not saying that it was not possible to know that DMF could degrade.**

    e. ZHP never identified the nitrosamine impurities in connection with its 2011 Risk Assessment and therefore did not evaluate the nitrosamine impurities as part of any steps of the risk assessment process.

(Stip. of ZHP, Ex. 4 (emphasis added)). [redacted]

[redacted].

ZHP has established the root causes of the contamination. The TEA and DMF introduced secondary amines to the processes—diethylamine ("DEA") and dimethylamine ("DMA") in the case of TEA, and DMA in the case of DMF, both as an impurity of the commercially purchased solvents and as degradation products of the solvents during the tetrazole ring formation step in the processes. The nitrous acid used to quench the sodium azide during a later step reacted with the amines to form NDMA in combination with the DMA and to form NDEA in combination with the DEA. [redacted]

[redacted]

[redacted]

(PRINSTON00075810-75811, PRINSTON00075854, Ex. 5).

These chemical reactions were clearly knowable. [redacted]. For example:

- "DMF sold commercially contains trace amounts of methanol, water, formic acid, and dimethylamine." (Xue Dep. 126:17-19, Ex. 26 (quoting Long & Meek, *Concise International Chemical Assessment Document 31: N,N-Dimethylformamide* (WHO 2001), Ex. 24); Xue Dep. 165:22-166:3, 184:1-185:8 (quoting Juillard, *Dimethylformamide:*

Purification, Tests For Purity And Physical Properties, Int'l Union of Pure and Applied Chem (Pergamon Press 1977), Ex. 25)).

- "In addition to secondary amines, however, a wide variety of tertiary amines have also been demonstrated to react with nitrous acid to produce N-nitrosamines in aqueous solutions." (Xue Dep. 282:20-283:1 (quoting Sun, Liu, and Zhong, *Theoretical Investigation of N-Nitrosodimethylamine Formation from Nitrosation of Trimethylamine*, J. Phys. Chem. A. 114, 455-465 (2010), Ex. 27).
- "The nitrosation of secondary amines has already been extensively studied, and the DMA has been confirmed to be easily nitrosated into NDMA in an acidic nitrite solution." (Xue Dep. 290:17-22 (quoting Sun, et al. supra, at 5)).

ZHP never tested for nitrosamines as part of its risk assessment during the development of the processes. [redacted]

(PRINSTON00075811, Ex 5).

On July 27, 2017, a remarkable email was written by Jinsheng Lin, Ph.D. (Pls.' Trans., Ex. 6; ZHP's Trans., Ex. 7). [redacted] (ZHP 432, Ex. 8; ZHP 292, Ex. 9; Min Li 4/20/2021 Dep. Tr. 82:21-83:17, Ex. 10). As recited by Dr. Li, whose testimony as a Rule 30(b)(6) corporate representative is binding on ZHP, the email was sent to the following individuals:

- Jucai Ge, ZHP's Quality Assurance Director, API Division;
- Min Li, Vice-President of ZHP's Analytical Operations, including the Center for Excellence in Modern Analytical Technologies (CEMAT);
- Peng Dong, Deputy Director of ZHP's Technical Department;
- Lihong Lin, ZHP's Director of Regulatory Affairs;
- Tianpei Huang, Member of CEMAT;
- Wangwei Chen. Technician in the Technology Department;
- Wenquan Zhu, Director of ZHP's Analytical Operations;
- Wenbin Chen, Technical Director of Key Laboratory in ZHP's Analytical Operations;
- Yanfeng Liu, Deputy Director of ZHP's Regulatory Affairs;
- Peng Wang, Deputy General Manager of Production and Operations Center; and
- Wenling Zhang, Deputy Director of Production Department II.

(Min Li 4/20/2021 Dep. Tr. 82:86:10, Ex. 10).[3] Dr. Li testified that the email discussed an effort to identify an impurity that appeared to be a nitroso compound, formed during a project focused

[3] The email was only produced as a PDF copy in the custodial file of Min Li, with the metadata revealing a "date created" of June 14, 2018, and no other ZHP custodian was listed as a duplicate

on potential modification to the manufacturing process for Irbesartan. The email compares this impurity to the NDMA in valsartan. Dr. Li testified that the email stated in part:

> Through the secondary mass spectrometry analysis, it can be inferred that the extra NO substituent is in the cyclic compound fragment, and it is very likely that it is an N-NO compound; **it is similar to the N-nitrosodimethylamine that occurs in valsartan when quenched with sodium nitrite, and its structure is very toxic.**
>
> * * *
>
> If it is confirmed as the above speculated structure, then its toxicity will be very strong, and there will be an **extremely high GMP risk**. **This is a common problem in the production and synthesis of sartan APIs**.

(*Id.* at 87:19-88:7, 88:13-89:18 (emphasis added)). Everything stated in the email was accurate, but this information was not disclosed to any customer or regulatory authority.

[redacted] (ZHP00359798, Ex. 31; ZHP01390018, Ex. 16).

Once disclosure was finally made, the FDA commenced its investigation, issued form 483 observations during a for cause inspection that took place from July 23 to August 3, 2018, and resulted in the issuance of a Warning Letter dated November 29, 2018. (PRINSTON00077339,

custodian despite the fact that Dr. Li, Jucai Ge, Linda Lin, Peng Dong, Wenquan Zhu, Wenbin Chen, Yangfen Liu, Peng Wang, and Wenling Zhang were all custodians. Jinsheng Lin was eventually added as a custodian, but his file also lacked a copy of the email.

Ex 11). The Warning Letter identified a number of cGMP violations, and determined that the valsartan was adulterated as a result. The FDA also emphatically rejected ZHP's central defense, both then and now, that the chemical reactions could not have been foreseen or detected. In salient part, the Warning Letter states:

> This warning letter summarizes significant deviations from current good manufacturing practice (CGMP) for active pharmaceutical ingredients (API).
>
> Because your methods, facilities, or controls for manufacturing, processing, packing, or holding do not conform to CGMP, your API are adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 351(a)(2)(B).
>
> * * *
>
> In November 2011 you approved a valsartan API process change (PCRC - 11025) that included the use of the solvent DMF. Your intention was to improve the manufacturing process, increase product yield, and lower production costs. However, you failed to adequately assess the potential formation of mutagenic impurities when you implemented the new process. Specifically, you did not consider the potential for mutagenic or other toxic impurities to form from DMF degradants, including the primary DMF degradant, dimethylamine. According to your ongoing investigation, dimethylamine is required for the probable human carcinogen NDMA to form during the valsartan API manufacturing process. NDMA was identified in valsartan API manufactured at your facility.
>
> You also failed to evaluate the need for additional analytical methods to ensure that unanticipated impurities were appropriately detected and controlled in your valsartan API before you approved the process change. **You are responsible for developing and using suitable methods to detect impurities when developing, and making changes to, your manufacturing processes. If new or higher levels of impurities are detected, you should fully evaluate the impurities and take action to ensure the drug is safe for patients**.
>
> **Your response states that predicting NDMA formation during the valsartan manufacturing process required an extra dimension over current industry practice, and that that your process development study was adequate. We disagree. We**

> **remind you that common industry practice may not always be consistent with CGMP requirements and that you are responsible for the quality of drugs you produce**.

(PRINSTON00077339, 77342 (emphasis added)).

[redacted] (Afnan 2/8/2023 Dep. Tr. 267:23-269:13). The Court has described Mr. Chesney's report in its Daubert decision: "[I]t reads like expert testimony rebutting liability claims." (ECF 2261, at 75). Mr. Chesney was shown the scientific literature utilized in the depositions of ZHP witnesses, including the IARC Monograph on the Evaluation of Carcinogenic Risk of Chemicals to Humans, *Some N-Nitroso Compounds*, Volume 17, dated May of 1978. (Chesney 3/21/2022 Dep. Tr. 117:3-10, Ex. 12). "[P]age 36 of this IARC monograph, the third full paragraph … says, '**It has been known since 1865 that the reaction of dimethylamine hydrochloride with sodium nitrate at an acidic pH yields N-nitrosodimethylamine,**'" which is NDMA. (*Id.* at 118:16-23).[4] **Mr. Chesney conceded that this is "the sort of thing I would expect scientific experts with whom I would collaborate to take into consideration**." (*Id.* at 119:12-14).

Mr. Chesney **agreed** that the FDA's November 2018 Warning Letter to ZHP, "summarizes significant deviations from current good manufacturing practices (CGMP) for active pharmaceutical ingredients (API)." (*Id.* at 320:24-321:6). The Warning Letter pointed directly to ZHP's failure to conduct a basic analysis of the potential chemical reactions in the manufacturing

[4] The root cause of the NDMA is the reaction of dimethylamine and nitrous acid during the quenching phase of the process. [redacted] (Min Li 4/20/2021 Dep. Tr. 76:14-24, Ex. 10).

process, specifically its "[f]ailure to evaluate the potential effect that changes in the manufacturing process may have on the quality of your API." (*Id.* at 328:6-12). Mr. Chesney agreed that **"[t]he failure to adequately assess the potential formation of mutagenic impurities when ZHP implemented the new process, that would be a cGMP violation."** (*Id.* at 329:9-331:16).

Second, the FDA stated in the Warning Letter, "You also failed to evaluate the need for additional analytical methods to ensure that unanticipated impurities were appropriately detected and controlled in your valsartan API before you approved the process change," and **Mr. Chesney confirmed that this was a cGMP violation**. (*Id.* at 331:17-332:5). The FDA also pointedly told ZHP: "You are responsible for developing and using suitable methods to detect impurities when developing, and making changes to, your manufacturing processes. If new or higher levels of impurities are detected, you should fully evaluate the impurities and take action to ensure the drug is safe for patients." Mr. Chesney agreed that this "was an obligation of ZHP." (*Id.* at 332:7-21).

Mr. Chesney conceded that the FDA "disagree[s] with ZHP [that predicting NDMA formation during the valsartan manufacturing process] required an extra dimension over current industry practice." (*Id.* at 334:8-16, 335:3-10). Related, the FDA noted, **"We remind you that common industry practice may not always be consistent with CGMP requirements and that you are responsible for the quality of drugs you produce,"** and **Mr. Chesney agreed that this was ZHP's responsibility**. (*Id.* at 335:12-336:2). Mr. Chesney admitted that ZHP violated cGMPs with respect to the zinc chloride process, rendering all of the valsartan-containing drugs manufactured with that process adulterated. (*Id.* at 321:7-15). Mr. Chesney agreed, **"[R]isk assessment is not a static process, it's a process that continues through the lifecycle of the drug's production and manufacture," and "[i]f they are aware that a product contains a contaminant that poses an actual or potential danger to health, and tell no one and continue**

to ship it anyway, that could be construed later, after evaluation of all the facts, as having shipped a contaminated and, therefore, adulterated product in interstate commerce." (*Id.* at 189:24-190:3, 195:16-23). [redacted]

[redacted]

Against this backdrop, Plaintiffs now seek to preclude the methodologically unsound opinions of Dr. Afnan.

THE *DAUBERT* STANDARD

The admissibility of expert testimony is determined pursuant to Federal Rule of Evidence 702. "As a gatekeeper, courts are supposed to ensure that the testimony given to the jury is reliable and will be more informative than confusing." *In re Zoloft (Sertraline Hydrochloride) Prods. Liab. Litig.*, 858 F.3d 787, 800 (3d Cir. 2017). Additionally, "[b]oth an expert's methodology and the application of that methodology must be reviewed for reliability." *Id.* at 791. The "specific way an expert conducts such an analysis must be reliable; '**all of the relevant evidence must be gathered**, and **the assessment or weighing of that evidence must not be arbitrary**, but must itself be **based on methods of [the relevant field].**'" *Id.* at 796. Here, there is no identifiable methodology, and the expert's approach, whether described as a methodology or an approach, is fatally flawed.

The party offering the proposed expert testimony bears the burden of establishing the admissibility of the testimony by a preponderance of the evidence. *Padillas v. Stork-Gamco, Inc.,* 186 F.3d 412, 417-18 (3d Cir. 1999). An "expert's opinions must be based on the methods and procedures of [the relevant field], rather than on subjective belief or unsupported speculation." *In re Paoli R.R. Yard PCB Litigation*, 35 F.3d 717, 742 (3d Cir. 1994) (citations and internal quotations omitted). Thus, "the expert must have 'good grounds' for his or her belief." *Id.*

(quoting *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 509 U.S. 579, 590 (1993)). These good grounds must support each step of the analysis and, "*any* step that renders the analysis unreliable under the *Daubert* factors renders the expert's testimony inadmissible." *Id.* at 745. A court should also consider the methodology's error rate when assessing its reliability. *Id.* at 742 n.8. Judges within this Circuit also consider how and when the methodology is used outside of litigation. *Id.* at 742 (discussing reliability factors under *Daubert* and Third Circuit case law).

Furthermore, "*Daubert*'s gatekeeping requirement .... make[s] certain that an expert, whether basing testimony upon professional studies or personal experience, employs in the courtroom the same level of intellectual rigor that characterizes the practice of an expert in the relevant field.'" *Elcock v. Kmart Corp.*, 233 F.3d 734, 746 (3d Cir. 2000) (quoting *Kumho Tire Co. v. Carmichael*, 526 U.S. 137, 152 (1999)); *see also Magistrini v. One Hour Martinizing Dry Cleaning*, 180 F. Supp. 2d 584, 594 (D.N.J. 2002*), aff'd,* 68 Fed. Appx. 356 (3d Cir. 2003). In addition, the following factors are relevant when determining reliability:

> (i) whether the expert's proposed testimony grows naturally and directly out of research the expert has conducted independent of the litigation; (ii) whether the expert has unjustifiably extrapolated from an accepted premise to an unfounded conclusion; (iii) whether the expert has adequately accounted for alternative explanations.

Magistrini, 180 F. Supp. 2d at 594–95 (internal citations omitted). To this end, the Third Circuit has affirmed the exclusion of expert testimony that "failed to consistently apply the [relevant fields'] methods … articulate[d], … deviated from or downplayed certain well-established principles of [the] field, and … inconsistently applied methods and standards to the data so as to support [an] a priori opinion." *Zoloft*, 858 F.3d at 792. The same outcome is required on this record.

I.

DR. AFNAN IS NOT QUALIFIED TO PROVIDE CHEMISTRY OR TOXICOLOGY OPINIONS

An expert must be qualified to offer the proffered opinions. [redacted] Based on this, Dr. Afnan cannot offer opinions in the fields of organic chemistry or toxicology.

II.

DR. AFNAN'S OPINIONS SHOULD BE PRECLUDED PURSUANT TO *DAUBERT*

Dr. Afnan's report [redacted]. (Afnan Amended R., Ex. 13). Dr. Afnan [redacted]. *See Paoli*, 35 F.3d at 742; *In re Mirena IUS Levonorgestrel-Related Prods. Liab. Litig. (No. II)*, 341 F. Supp. 3d 213, 241 (S.D.N.Y. 2018) (holding, **"[M]ethodology ... aimed at achieving one result ... is unreliable, and ... must be excluded."** (quoting *Faulkner v. Arista Records LLC*, 46 F. Supp. 3d 365, 381 (S.D.N.Y. 2014)).

In granting a motion to preclude an expert under *Daubert*, this Court has observed:

> [C]ourts also need not admit mere conclusions or opinion evidence that is connected to existing data only by the *ipse dixit* of the expert. A court may conclude that there is simply too great an analytical gap between the data and the opinion proffered…. Mere assumptions, without causal evidence or methodological analysis may be inadmissible.... Conclusions based only on the expert's experience, and testimony founded on methods that are not generally accepted or lack testable hypotheses may also fail to surmount the *Daubert* standard.

Player v. Motiva Enterprises LLC, No. Civ. 02–3216(RBK), 2006 WL 166452, at *6-7 (D.N.J. Jan. 20, 2006) (citations omitted), Ex. 14. In *Player*, this Court found the expert failed to satisfy the reliability requirement, as the expert failed to consider important facts without satisfactory explanation, among other things. *Id.* at *7. The Court held: "His method is untestable and arbitrary, without a generally accepted, established, or peer reviewed methodology, and his evaluation was conducted without any real standards." *Id.* at *8. Here, [redacted]

A. [redacted]

[redacted] (Afnan 2/8/2023 Dep. Tr. 29:24-32:5, 35:8-37:13). [redacted] (*Id.* at 31:22-32:10). [redacted]

[redacted]

(*Id.* at 37:16-40:15). [redacted]

The significance of these SOPs cannot be reasonably disputed. [redacted]

[redacted]

(Peng Dong 3/29/2021 Dep. Tr. 33:13-19, 34:22-35:1, 41:14-24, 42:3-11, 42:13-43:4, 45:23-46:9, Ex. 15). [redacted]

[redacted] (Minli Zhang 3/23/2021 Dep. Tr. 181:23-194:7, Ex. 19; ZHP00703030, Ex. 17).

[redacted] *See Zoloft*, 858 F.3d at 796; *Mirena II*, 341 F. Supp. 3d at 242. This gap in his "methodology" is too large to be overcome. "**Where an expert ignores evidence that is highly relevant to his [or her] conclusion, contrary to his [or her] own stated methodology, exclusion of the expert's testimony is warranted.**" *Mirena II*, 341 F. Supp. 3d at 242 (quoting *In re Rezulin Prod. Liab. Litig.*, 309 F. Supp. 2d 531, 563 (S.D.N.Y. 2004)).

B. [redacted]

[redacted]. (Afnan Amended R. 5, Ex. 13). [redacted] (Afnan 2/8/2023 Dep. Tr. 77:1-16). [redacted]

[redacted]

(*Id.* at 308:11-24 (emphasis added)). [redacted]

(*Id.* at 308:11-310:24). [redacted]

(*Id.* at 318:9-319:9). [redacted]

(*Id.* at 319:13-320:20). [redacted]

[redacted] (*Id.* at 320:21-322:9). [redacted]

[redacted] (*Id.* at 328:15-329:9). [redacted]

[redacted]

(Afnan 2/8/2023 Dep. Tr. 332:16-336:2).

[redacted] (*Id.* at 326:19-328:11). [redacted] (*Id.* at 329:10-332:14). [redacted] (*Id.* at 326:9-17).[5] [redacted] (Peng Dong 4/1/2021 Dep. Tr. 377:13378:7, 385:23-396:6, Ex. 20).

[redacted]"[6] (Afnan 2/8/2023 Dep. Tr. 298:15-299:1, 300:18-301:19).

[redacted]

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5 [redacted] (HUAHAI-US00007752, Ex. 21; PRINSTON00080011, Ex. 22).

6 [redacted] (PRINSTON00077342, Ex. 11).

[redacted] (Afnan 2/8/2023 Dep. Tr. 77:18-78:5). [redacted] (*Id.* at 79:16-82:9). That is why the changes from the branded process obligated ZHP to do a cGMP compliant risk assessment, and why his analysis is completely unsound.

C. [redacted] (PRINSTON00075809, Ex. 5). [redacted] (Afnan 2/8/2023 Dep. Tr. 108:4-113:8). [redacted] (*Id.* at 201:15-202:5).

[redacted]

[redacted] (*Id.* at 99:22-100:19, 105:3-21). [redacted]

> DMF sold commercially contains trace amounts of methanol, water, formic acid and dimethylamine.
>
> * * *
>
> Formic acid and dimethylamine are thus predominant impurities in DMF and determine the odor of the impure solvent.
>
> * * *
>
> Owing to its various modes of degradation, hydrolysis, thermal and photochemical decomposition, the principal impurities found in DMF are: dimethylamine, formic acid, hydrogen cyanide, carbon monoxide.

(*Id.* at 123:8-16, 130:13-19, 155:11-17 (quoting Long & Meek, *Concise International Chemical Assessment Document 31: N,N-Dimethylformamide* (WHO 2001), Ex. 24; Juillard, *Dimethylformamide: Purification, Tests For Purity And Physical Properties*, Int'l Union of Pure and Applied Chem (Pergamon Press 1977), Ex. 25)).[7] [redacted] (Afnan 3/8/2023 Dep. Tr. 114:9-24).

[redacted]

[7] A 2012 Certificate of Analysis for the triethylamine [redacted] which was located on the internet, indicated the presence of DEA as an impurity of the product as sold. (Zhejiang Jianye Chem. Co., Cert. of Analysis: Triethylamine (2012), Ex. 23). [redacted]

[redacted]. (*Id.* at 129:19-131:17). [redacted]

[redacted] (Xue Dep. Tr. 131:7-14, 208:24-209:5, Ex. 26).

D. Dr. Afnan's Inadequate Consideration of FDA Actions.

[redacted] This goes far beyond issues for a jury to weigh.

[redacted]. Thus, the method that yielded the contrary opinion in the report should be scrutinized quite closely. *See In re Zoloft Products Liability Litigation,* 26 F. Supp. 3d 449, 460-61 (E.D. Pa. 2014) (citing *In re Rezulin Products Liability Litigation,* 369 F. Supp. 2d 398, 425 (S.D.N.Y. 2005) **("[I]f the relevant scientific literature contains evidence tending to refute the expert's theory and the expert does not acknowledge or account for that evidence, the expert's opinion is unreliable.**")). The same reasoning should apply here where the expert disagrees with the FDA's conclusion.

[redacted]

(Afnan 2/8/2023 Dep. Tr. 112:18-24).

[redacted] (*Id.* at 53:9-57:2). [redacted] (Afnan 3/8/2023 Dep. Tr. 75:7-22, 173:19-174:6). [redacted] the USP addresses this exact point. "Nonmonograph tests and acceptance criteria suitable for detecting and controlling impurities that may result from a change in the processing methods or that may be introduced from external sources should be employed in addition to the tests provided in the individual monograph, where the presence of the impurity is inconsistent with applicable good manufacturing practices or good pharmaceutical practices." USP General Notice Requirements, Revision Bulletin, Section 5.60, April 1, 2015, Ex. 32. [redacted] (Afnan 3/8/2023 Dep. Tr., 182:2-185:21, 386:2-389:8). [redacted]

[redacted]

(*Id.* at 391:22-392:15). [redacted]

[redacted]

(*Id.* at 369:22-371:5). There is no methodology or analysis underlying this obviously inaccurate opinion and that opinion should be precluded.

Moreover, one of the FDA statements attributed to then FDA head Scott Gottlieb [redacted] to suggest that the FDA excused ZHP's conduct explicitly contradicts his assumption. The FDA statement actually recites the issuance of the Warning Letter to ZHP and points out that these violations were consequential: "We've placed a ZHP facility on import alert to stop all of its API and finished drugs made using ZHP's API from legally entering the United States. We also issued them a warning letter outlining **several manufacturing violations**, **including impurity control, change control and cross-contamination from one manufacturing process line to another**. (*Id.* at 252:11-24 (quoting January 25, 2019 FDA Statement, at 2, Ex. 28) (emphasis added)). [redacted] In fact, as stated the violations were so significant that the FDA issued an Import Alert precluding the import of any drug products from ZHP's cGMP riddled operations until the serious violations could be corrected. (ZHP00061080, Ex. 29).

In another salient and related example of this "see no evil" approach, [redacted] (Afnan 3/8/2023 Dep. Tr. 374:5-375: 12). [redacted] (*Id.* at 375:13-377:10, 379:10-21). [redacted]

[redacted] (*Id.* at 379:23-380:21). Dr. Afnan's methodology to deny wrongdoing at all costs, without any analysis or rational basis, is unreliable.

E. [redacted]

(*Id.* at 359:20-361:1, 361:22-362:9396:9-397:2, 401:2-9). This flawed circular reasoning is completely unreliable.

[redacted] (*Id.* at 196:10-20). There is no rigor to this conclusion driven analysis.

F. Additional Methodological Flaws.

Another flaw in Dr. Afnan's approach is [redacted]. (*Id.* at 109:17-114:7, 171:21-173:16, 366:16-367:1). This position is so flawed that it requires no analysis, and should be precluded.

Dr. Afnan's reliance on the opinions of Dr. Xue, ZHP's expert in organic chemistry, is also problematic. [redacted]. (*Id.* at 156:6-24, 171:3-5, 206:9-15, 213:17-20, 231:3-6). [redacted] (*Id.* at 175:22-176:5). Thus, if Dr. Xue's opinion on that point (or more) is precluded, any opinion formed in reliance on that opinion would of necessity also be precluded. *Paoli*, 35 F.3d at 742 (an "expert must have 'good grounds' for his or her belief"); *In re TMI Litig.*, 193 F.3d 613, 697 (3d Cir, 1999) (holding, "If the data underlying the expert's opinion are so unreliable that no reasonable expert could base an opinion on them, the opinion resting on that data must be excluded.").

[redacted]

[redacted]. Simply put, an expert cannot gather its own ex parte hearsay evidence that is unavailable to all parties, and rely on that "evidence" at trial—in an effort to subvert the factual record developed through court ordered discovery. *Paoli*, 35 F.3d at 742-43 (an "expert must have 'good grounds' for his or her belief, and "the expert's testimony must assist the trier of fact," who will only hear facts developed in the record); *TMI Litig.*, 193 F.3d at 697 (holding, "If the data underlying the expert's opinion are so unreliable that no reasonable expert could base an opinion on them, the opinion resting on that data must be excluded."). Dr. Afnan should be precluded from relying on the ex parte interviews, and any opinions based on those interviews should be precluded.

Moreover, when confronted with the clear language of the July 27, 2017 email, [redacted] (Afnan 3/8/2023 Dep. Tr. 230:5-18). Of course, the formation of the NDMA as a result of the sodium nitrite quenching process is not debatable, and [redacted] (Min Li 4/20/2021 Dep. Tr. 96:12-16). [redacted] (Afnan 3/8/2023 Dep. Tr. 230:20-231:6). He cannot provide a reliable opinion without a reliable assumption as to how the NDMA was formed.

[redacted] (*Id.* at 234:15-235:2). [redacted]

[redacted] (*Id.* at 235:19-236:7). A methodology that leads to any answer but "Yes" to that question is flawed as a matter of law.

[redacted]. (*Id.* at 413:22-415:16; FDA Letter to Valisure, dated December 5, 2022, Ex. 30). [redacted] (Afnan 3/8/2023 Dep. Tr. 412:8-413:4). [redacted] (Xue Dep. Tr. 171:6-10, Ex. 26), [redacted] (Afnan 3/8/2023 Dep. Tr. 416:24-419:8). [redacted]

CONCLUSION

Dr. Afnan's opinions are hopelessly flawed, from top to bottom. For the foregoing reasons, Ali Afnan, Ph.D should be precluded from offering any opinions in this case.

Respectfully,

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